REMARKS

Reconsideration of the allowability of the present application in view of the above amendments and the following remarks is requested respectfully.

Status of the Claims

Claims 1 and 4 to 18 were acted upon by the Examiner. Claims 1 and 4 have been cancelled without prejudice. Claims 5, 9, 11, 12, and 16 have been amended. Claims 23 to 32 have been added. Accordingly, Claims 5 to 18, and 23 to 32 are presented for examination.

Support for New Claims

Support for Claims 23 to 32 may be found throughout the application, particularly in Examples 1 and 2 (Page 8, line 35, to page 11, line 15, of the application).

Arguments

A. The Rejection of Claims 1, 4, 9, 10, and 12 Under 35 U.S.C. §102(a)

Claims 1, 4, 9, 10, and 12, directed to a method for increasing the tolerance of a mammal to transgenic cells, were rejected by the Examiner under 35 U.S.C. §102(a) as being anticipated by the disclosure of Smith et al., *Gene Therapy* (1996); 3:496-502 (Abstract only) (hereafter "Smith et al.") and, alternatively, by the disclosure of International Publication No. WO 96/12406.

Claims 1, and 4 to 15 have been cancelled without prejudice. Thus, the rejection of Claims 1, 4, 9, 10, and 12 under 35 U.S.C. §102(a) are moot.

B. The Rejection of Claims 1 and 4 to 18 Under 35.U.S.C. §112, Second Paragraph

Claims 1 and 16, and all claims dependent thereon, were rejected by the Examiner under 35.U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Claim 1 and all claims dependent thereon have been cancelled.

Applicants amend and traverse the rejection of Claim 16 as follows.

Claim 16 has been rejected for being indefinite because the Examiner asserts that it is unclear whether p15-deoxyspergualin is administered after discontinuing immunosuppressant therapy.

In response to this rejection, applicants have amended Claim 16 to recite "wherein said immunosuppressant is administered before, during or after, or any combination thereof, administration of the transgenic product". This amendment

clarifies that the p15-deoxyspergualin can be added before, during or after, or any combination thereof, administration of the transgenic cells. Support for this amendment is found in originally filed Claim 4. In view of this amendment applicants respectfully request withdrawal of the Examiner's §112, second paragraph, rejection of Claim 16 and all claims dependent thereon.

Claim 16 has been rejected for being indefinite because the Examiner asserts that the metes and bounds of the claimed invention are not clear because the specification does not define as to when or at what time after the administration of the transgenic cells and/or the immunosuppressant, the immunosuppressant therapy is discontinued.

Applicants traverse this rejection.

The Examiner is respectfully directed to Examples 1 and 2 in the specification. In Example 1, mice are treated with p15-deoxyspergualin for 21 days after administration of adenovirus. In Example 2, mice are treated with p15-deoxyspergualin for one day before administration of adenovirus and for 5 days thereafter. Thus, the specification provides various examples of when immunosuppressant therapy is discontinued. Given these teachings of from 5 to 21 days after adenoviral administration, the skilled artisan would need no further guidance in order to practice the claimed invention and there is no need for applicants to specifically claim an exact time when immunosuppressant therapy is discontinued. In view of this argument applicants respectfully request withdrawal of the Examiner's §112, second paragraph, rejection of Claim 16 and all claims dependent thereon.

Claim 16 has been rejected for being indefinite because the Examiner asserts that Claim 16 is vague because it is unclear as to what is the invention claimed since the

claim starts with "In a method..." and then recites the method.

In response to this rejection, applicants have amended Claim 16 to recite "A method..." instead of "In a method...". In view of this amendment applicants respectfully request withdrawal of the Examiner' s §112, second paragraph, rejection of Claim 16 and all claims dependent thereon.

Claim 16 has been rejected for being indefinite. The Examiner has based this rejection on the use of the term "the improvement" without antecedent basis.

In response to this rejection, applicants have amended Claim 16 to delete the term "improvement". In view of this amendment applicants respectfully request withdrawal of the Examiner's §112, second paragraph, rejection of Claim 16 and all claims dependent thereon.

C. The Rejection of Claims 1 and 4 to 18 Under the Enablement Requirement of Section 112, First Paragraph

Claims 1 and 4 to 18, directed to methods for increasing the tolerance of a mammal to transgenic cells, were rejected by the Examiner under the enablement requirement of 35 U.S.C. §112, first paragraph. According to the Examiner, the specification does not enable such a method when: (1) such transgenic cells are produced *in vitro*; (2) when the transgene of such transgenic cells produces a therapeutic protein that effects a treatment of a disease; or (3) when the transgenic cells produced *in vivo* after the administration of a vector *in vivo* produce treatment of any disease. Claims 1 and 4 to 15 have been cancelled without prejudice. Accordingly, Claims 16 to 18 remain rejected under 35 U.S.C. §112, first paragraph. As explained below, this rejection is traversed respectfully.

The Examiner has asserted that the specification is not enabling with regard to a method wherein transgenic cells are transplanted in a mammal or in a man because the state of the art of cell transplantation, except for autologous cell transplantation, is unpredictable. In response to this assertion, applicants have amended Claim 16 to recite "..a cell of said mammal...". Support for this amendment is found on Page 3, line 11, of the application, which recites, "Transgenic cells are cells of any type".

The Examiner has asserted that the specification is not enabling with regard to a method wherein transgenic cells comprising a transgene when the transgene of such transgenic cells produces a therapeutic protein that effects a treatment of a disease and that the specification is not enabling with regard to a method when the transgenic cells produced *in vivo* after the administration of a vector *in vivo* produce treatment of any disease. Applicants respectfully traverse this assertion.

The Examiner's rejection of the claims directed to gene therapy treatments and treatment of diseases using gene therapy is without basis. Gene therapy protocols are widely available and one of skill in the art would recognize that the claimed methods may be useful in gene therapy methods. Furthermore, it should be understood that the present claims recite "transgenic cells are produced in the course of a gene therapy treatment". A "gene therapy treatment" does not require a patient to be cured. Thus, even if a gene therapy regimen results in low expression of a therapeutically useful gene, such a low expression may still be of significant benefit to a patient, alleviating r slowing the effects of a given disease. For example, as shown in Example 2, AAT, which may be used to treat alpha-1 anti-trypsin deficiency, was shown to be expressed at increased and sustained levels after treatment with DSG.

Furthermore, the Examiner has asserted that Example 1 of the specification is

unclear. Applicants respectfully traverse this assertion. The Examiner has asserted because Bett et al. discloses more than one adenoviral vector, it is possible that the increased tolerance caused by DSG treatment in applicants' Examples may be due to a different vector being used for the DSG-treated mice. This assertion is without merit. In Example 1, a mouse, administered with an β-galactosidase transgene and treated with DSG, is compared with a control mouse, also administered with an β-galactosidase transgene but not treated with DSG. The results showed that the level of expressed β-galactosidase product in the DSG-treated mouse was significantly sustained and greater than the level of expressed β-galactosidase product in the control mouse. It is abundantly clear, therefore, that treatment with DSG was the cause of increased sustained expression of β-galactosidase product. It is inconsequential what other deletions/insertions the vector expressing β-galactosidase contained since the proper controls were utilized.

The Examiner raised a similar question respecting Example 2, which compares the level of expressed alpha-1 anti-trypsin (AAT) in a mouse administered with an AAT transgene and treated with DSG with the level of expressed AAT in a control mouse administered with the same AAT transgene but not treated with DSG. According to the Examiner, since the level of AAT expressed in Example 2 is greater than the level of beta-galactosidase expressed in Example 1 and since AAT is not antigenic, "...one could assume that the higher protein levels in example 2 could be due to lack of antigenicity of the transgene product."

Applicants fail to understand the basis of the Examiner's assertion. Generally, experimental procedure for testing the effect of treatment of a subject with a certain compound involves comparing, under the same conditions, a first subject, which has been treated by the compound in question (here DSG), with a control subject which has

not been treated by the compound in question. In Example 2, a mouse, administered with an AAT transgene and treated with DSG, is compared with a control mouse, also administered with an AAT transgene but not treated with DSG. The results showed that the level of expressed AAT product in the DSG-treated mouse was significantly greater than the level of expressed AAT product in the control mouse. It is clear, that DSG was the cause of increased sustained expression of AAT product. In contrast, it is not at all clear what the Examiner's rationale is in comparing the results of Example 2 with those of Example 1. Even if it were the case that the greater expression of AAT in Example 2 as compared to the expression of beta-galactosidase in Example 1 may be attributed to properties of AAT, it still can not be ignored that the level of expressed AAT in the mouse treated with DSG is significantly greater than the level of expressed AAT in the mouse not treated with DSG.

In regard to the routes of administration covered by the claims, applicants note that MPEP §2164.01 states that the test of enablement requires a determination as to whether one of skill in the art can practice the claimed invention without undue experimentation. Applicants note that such is the case. The claimed invention is a method for increasing the tolerance of a mammal to transgenic cells. One skilled in the art, seeking to practice such a method on a certain mammal containing a certain transgene can simply use the assay described on page 8 of the application to determine which immunosuppressant to use and in what amount, what route of administration, and how long such an immunosuppressant should be applied.

Given the guidance in the application as identified above and the level of skill in the art, Applicants submit that the claimed invention would not require undue experimentation. As stated in the MPEP, section 2164.06:

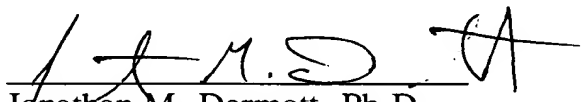
> "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni,* 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). " 'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.' " *In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt,* 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

Given the guidance in the Specification, the Examples section of the application, and methods known in the art, any experimentation necessary to determine an effective route of administration of an immunosuppressant would be routine for one skilled in the art in view of the more than reasonable guidance provided and the extensive guidance in the scientific literature on immunosuppressant administration. For example, one of skill in the art may follow examples 1 and 2 and substitute different therapeutic genes for the β-galactosidase and AAT genes used in these examples with the experiment directed towards a lowered immune response and a benefit to the patient by the expression of the transgene.

In view of this argument applicants respectfully request withdrawal of the Examiner's §112, second paragraph, rejection of Claim 16 and all claims dependent thereon.

A Petition for extending the period to respond to the Examiner's Action for two months, from October 30, 2003 to December 30, 2003, is enclosed.

Respectfully submitted,



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